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Study of Human Lactation for Effects of Environmental Contaminants: The North Carolina Breast Milk and Formula Project and Some Other Ideas

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The presence of environmental contaminant chemicals in human milk, their demonstrated toxicity, and the lack of data in human beings led to the North Carolina Breast Milk and Formula project, a three-center prospective birth cohort study of 856 children. In this study, we measure polychlorinated biphenyls (PCBs) and DDE in milk and other fluids, follow the course of lactation, and note growth, morbidity and development in the children. Lactation is hormonally complicated and has parts that are plausibly interfered with by contaminant chemicals, and certain kinds of morbidity that occur in breastfed children might also represent the result of chemical contamination of milk. Preliminary data analysis confirms the widespread presence of chemicals in milk; women with higher DDE levels do not breast-feed as long, but this is not true for women with higher PCBs. Besides this study, several case-control or survey-type studies, such as studies of failure to thrive, certain rashes, or short-term breast-feeding would be helpful. Laboratory studies of enzyme induction are now feasible in children and might be a very sensitive if not totally specific endpoint for study of PCBs in milk.

Introduction

The widespread occurrence of environmental chemical contaminants or drugs in human milk is the subject of several recent reviews (*1–4*), as well as a topic in this symposium; for our purposes, we will accept it as given. The toxicity of the chemicals present in milk is also detailed here and in the literature (*5*); we will not review it further. The topics here will be, then, given universal prevalence of low-level chemical contamination of milk and nonspecific toxicity of the contaminants, how can toxicity best be studied in humans? To answer this, we analyze the physiology of lactation to identify disruptable parts, and we examine the clinical course of nursed children to identify vulnerable points or morbidity that might be attributable to the chemicals in question. Since we are involved with a large clinical study in which we measure polychlorinated biphenyls (PCBs) and 2,2-bis(4-chlorophenyl)-1, 1-dichloroethylene (DDE) in milk and gather morbidity data, we will discuss these questions in the context of the design and conduct of that study, as well as present some preliminary results from it. There are other questions that our study does not address, and we will mention some of those. Finally, we will consider some of the estrogenic properties of PCBs and DDE; estrogenicity is a mechanism by which some of our findings can be plausibly interpreted.

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Endocrinology of Lactation

The initiation of lactation in humans is tied to the hormonal events at the termination of pregnancy; however, the anatomic and secretory stage is set at puberty. In contrast to rodents, humans do not require the full hormonal expression of pregnancy for full lactation, since lactation has been reported after delivery at 4 months or abortion at 3 months. However, during normal pregnancy, the ductules, lobules (secretory units) and alveoli (collecting units) hypertrophy, and new lobules are formed under the influence of estradiol and progesterone, and probably also adrenal corticosteroids. Differentiation of the alveolar lining cells begins at the end of the first trimester, and a secretory histology is present from the fourth month on. Estrogens alone can cause hypertrophy in breast tissue; they act synergistically with prolactin during pregnancy (*6*). Prolactin concentrations begin to rise very early in

pregnancy, before milk secretion can be established. They remain high for the first few days or weeks postpartum whether or not breast-feeding is done. Prolactin is essential for initiation of lactation; women treated with bromocriptine (which selectively inhibits the secretion of prolactin) or who have Sheehan's syndrome (hypopituitarism from postpartum necrosis of the pituitary) do not lactate. After the third postpartum week, prolactin concentrations vary and seem to be related to suckling stimulation. The high concentrations present at term are not maintained (*7*).

The very high concentrations of estrogens and progesterone that support pregnancy fall precipitously at term, and this disappearance correlates with the beginning of lactation. Given postpartum, estrogens such as diethylstilbesterol (DES) or estradiol inhibit lactation but do not alter prolactin secretion. It thus appears that estrogens are peripheral lactation inhibitors, even when the breast is stimulated by prolactin. This may be the mechanism seen in the more subtle effect of contraceptive estrogens, which decrease the duration of lactation (*8*). Lactation is a time of relative estrogen deficiency. Postpartum amenorrhea is more prolonged in breast-feeders (*9*).

Prolactin stimulates milk production. Oxytocin stimulates milk ejection. It is secreted in response to suckling, although concentrations are very low and hard to measure. The letdown, or milk ejection reflex, is probably oxytocin-mediated. Letdown does not require actual contact with the infant in humans or animals; the sight of an infant, or the sound of its cry can elicit the response. Presumably, some of the impact of psychological or emotional disturbance on breast-feeding is mediated through interference with this response. Oxytocin is essential for milk ejection in humans, but not in all animals. In rats, the oxytocin-induced milk ejection reflex is decreased by estrogen (*7*).

Introduction of foods other than breast milk (weaning) is presumably accompanied by less efficient emptying of the breasts. Although there is storage space for perhaps 48 hr of production, distention of the alveolar sacs results in decreased milk synthesis. Involution of breast tissue is apparently governed predominantly by local factors, and what role hormones play is not clear (*7*). Prolactin appears to inhibit luteotropin-releasing hormone, and thus the release of luteinizing hormone and follicle-stimulating hormone, and about half of all women do not menstruate until they have weaned completely (*6*). At some point, however, menses return. Some women lactate through several ovulations; indeed, women in our study occasionally report that the reason that they weaned one child was that they were pregnant with another. Serial pregnancies have been reported with uninterrupted lactation (*10*).

Clinical Characteristics of Breast-Fed Children

The percentage of mothers who try to breast-feed at least partially is increasing. Formula manufacturers periodically attempt counts. Annual surveys done by Ross Laboratories from 1955 through 1979 show that in 1970, 25% of children were breast-fed completely at one week and 6% were still getting some breast milk at 6 months; for 1979, the figures were 50% and 23% (*11*). Although young, white, college-educated women are most likely to breast-feed, there have been increases in all age and race groups in these data. The degree of encouragement offered to a mother to breast-feed and the enthusiasm and expertise that back it up are quite variable; there is some evidence that successful breast-feeding is aided by knowledgeable social support (*12*).

There is consensus that the goal of medical recommendations is to increase breast-feeding (*13*). Most recommendations made by and to organizations concerned with infant nutrition, such as the American Academy of Pediatrics (*14*) and the World Health Organization (*15*), are for breast milk for everyone. There is general agreement that a child can be totally breast-fed for the first 6 months of life by a healthy mother; supplemental vitamins K and D (*16*) in the newborn period and iron are generally recommended. Some babies breast-feed for a year or so, are weaned directly to a cup, and seem to do fine. The empirical basis for the recommendations is variable and depends strongly on whether developing or developed countries are under discussion. In the Third World, there are situations where there is neither money to buy adequate supplies of formula nor clean water with which to prepare it, and where there is substantial infant mortality from diarrheal diseases against which breast-feeding offers defense. The marketing of formula in the third world is a matter of intense controversy (*17–19*). In the United States, there is evidence that children have lower risks of lower respiratory tract infections (*20*) and hospitalizations for gastroenteritis (*21*) while being breast-fed. There is mixed evidence about the frequency of allergies in breast-fed children with a strong family history of atopy (*22*). There is much laboratory evidence concerning the presence in milk of IgA, white cells, and other substances that ought to be beneficial (*23*). In addition, there are appeals to ease and convenience, resistance to spoilage, and Darwinian biology.

There are some unresolved issues. Not all women seem to be able to breast-feed satisfactorily, as judged either by a reasonably steep growth curve or a reasonably silent, happy child. Such troubles, termed "failure to thrive at the breast" (*24,25*), can occur despite adequate nutrition, motivation, and support. Breast-fed children are lighter than bottle-fed children, and they become more so the longer they are breast-fed (*26*). From a simple calorie intake point of view, this is not surprising. Milk production in most women does not exceed about 800 mL/day, although there are a few exceptions (*27*). Thus the calories to support more rapid growth are simply not there (*28*). This observation has caused some controversy; the argument has been made that the growth of the totally breast-fed child is optimal in some sense (*29–31*), and that this more appropriate early growth rate is protective against later obesity, the

most common nutritional disorder in developed countries. There is no empirical support for this claim.

Some women secrete in their milk a pregnanediol which is absorbed by the child and which inhibits glucoronization of bilirubin (*32*). At about the fourth week of life, such children develop bilirubins of two to three times normal, which decline if breast-feeding is stopped (*33,34*). It is claimed that such children can be put back on the breast after several days and that the condition will not recur (*35*). Some breast-fed children have prolonged physiologic jaundice in the neonatal period; it is sometimes the practice to supplement with water or wean them. It is not clear that such prolongation occurs more frequently in breast-fed than in bottle-fed children, nor is there evidence for the effectiveness of supplementation (*34,35*). Finally, there are animal models in which vertical transmission of virus associated with mouse mammary tumors occurs from mother to daughter through milk; the offspring then have higher rates of mammary tumors. This is a very difficult issue to study epidemiologically, but the evidence seems to be that human breast cancer is not virus-induced, and that, while daughters of women with breast cancer do have a higher rate, it is independent of whether or not they were breast-fed (*36*).

Studying Breast-Feeding for Effects of Pollutants in Milk

Breast-feeding is thus subject to a complex interplay of hormonal, social, medical and other forces, and its normal course might plausibly be interfered with by some deleterious substance either through an effect on the mother or on the child. Given the all but universal contamination of milk and the demonstrated biological activity of the chemicals in question, the notion of toxicity cannot be ruled out. Any calculation of dose to the breast-fed child yields daily consumptions that regularly exceed Allowable Daily Intake guidelines (*2*), and in fact overlap the doses at which toxicity like enzyme induction can be shown to occur in the laboratory (*37*). Nevertheless, there is substantial observation of the clinical course of breast-fed children in developed countries, and they do not as a rule develop chloracne, fail to grow, appear to be immunodeficient, or handle drugs in an observably inferior way to bottle-fed children. When we designed the current study, then, our suspicion was that readily seen toxicity was unlikely, and thus that any study was likely to be negative. However, a persuasively negative study would be useful, given the suspicions raised on toxicological grounds and the prevalence and magnitude of contamination.

The straightforward way to study the effects of contaminated breast milk is to identify a cohort, document its exposure, and follow it over time, noting illnesses, growth, development, or any other phenomena as they occur. While straightforward, this approach has obvious disadvantages. It takes a long time, it has low power to detect associations between exposures and rare events unless the associations are very large, and it is expensive in both dollars and investigator time. We thus thought about several design alternatives that are quicker, cheaper or both.

A quicker method is to study breast-fed children and bottle-fed children retrospectively. The assumption behind such a design is that all breast-fed children are exposed to contamination and bottle-fed children are not. We could decide what criteria were necessary to be called breast-fed, say, no more than one bottle per day to 6 weeks with some breast-feeding to 6 months, and have the bottle-fed group be totally bottle-fed. We would then pick an age, say, 6 months, at which cases and controls would be identified, and look retrospectively at weight gain, frequency of infection, birth weight, etc. The problem with this kind of study is that it is biased in favor of breast-feeding (*38*), but to an unmeasurable degree. Children who remain breast-fed to 6 months represent a subset of the children who started, and they are mostly the ones who have done the best. Children who become ill or fail to gain weight while being breast-fed are usually supplemented or weaned. Such children would not appear in either group in a study like this, yet it is among them that much of the total morbidity is occurring. Such a study would thus be likely to show no effect of contaminated milk, but could not be persuasive, however large it was.

Another quicker possibility was cross-sectional or survey designs. Children of various ages could be identified; various aspects of their health could be studied, their method of feeding could be determined, and their mother's milk could be tested. Unfortunately, the results of such testing would be difficult to interpret. Women start with a certain concentration of chemicals in their milk, but over the course of lactation, some of the chemicals will be transferred to their child. Thus the measured concentration of chemicals would depend on the age of the child and the amount of breast-feeding that was done, as well as the woman's initial concentration. It would be difficult to determine whether the child of a woman with a low current concentration had always been exposed to a low concentration or had previously been exposed to a high one.

Often in epidemiological work, the fastest and most powerful technique is a case-control study. In such a design, some illness is picked, such as acneform rash, failure to thrive, or frequent infections, and contaminated breast milk is sought as a risk factor. Because of its retrospective nature, such a design would suffer from the same difficulties mentioned above. In addition, no single illness is under suspicion, so taking such an approach would involve a series of studies of different illnesses; alternately, we would need to know ahead of time what illness or condition was most sensitive to the chemicals. In either case, such a design would still leave open questions about unstudied illnesses.

Before facing the necessity of a live cohort study, one option remained; perhaps a paper cohort, rather than a real one, could be followed. In these kinds of studies,

records routinely generated for clinical or other purposes are examined, rather than the actual patients. Such studies are laudable in their simplicity, and when it happens that the information that has been gathered is the information you want, they can be quite efficient and timely. We could not find, however, any group of children on whom records had been kept and from whom breast milk samples had been collected in such a way that we could go back and analyze them.

The North Carolina Project: Design

This exhausted our alternate studies, so we set about the design of a longitudinal study. The basic question to be answered was of a dose–response nature. We therefore needed to look at dose and some of its determinants, identify and document the most plausible responses, and get information on other factors that might confound the relationship between the two.

All children are exposed transplacentally. The additional dose to the breast-fed child is a combination of concentration of contaminant chemicals, volume per unit time, and duration of breast-feeding. Measurement of the first presented technical problems, ultimately solved by our chemists (*39*). Since we were going to the trouble of analyzing breast milk, we also collected and analyzed samples of maternal and cord blood, placenta and some formula. Determinants of maternal concentration are things like diet of the mother, occupation, cigarette and alcohol use, weight, age and some demographic characteristics. Volume of breast milk consumed is a problem, since the only reliable way to measure it is individual test weighings before and after all feedings. This was not logistically possible, and we have had to make an assumption that the variation in the amount of milk consumed per day does not overwhelm the variation in contaminant concentration. Duration is not a totally clean endpoint, in that women vary a great deal in their weaning practices and do not abruptly stop complete breast-feeding and go to other foods.

Proposed response measures were more difficult. From animal studies and human data, we constructed a list of possible outcomes. Effects at birth due to transplacental exposure were low birth weight, hyperbilirubinemia, hepatosplenomegaly, acne, pigmentation, natal teeth, and perhaps some delay in central nervous system development. Later effects would be similar; they include poor weight gain, increased frequency of infection, certain rashes or pigmentation, hepatosplenomegaly, and delay in central nervous system development. All of these might show up as a tendency for mothers to breast-feed for shorter lengths of time. Most of this information is of the kind gathered routinely during well-child care and can be obtained by a simple physical examination of the child, a medical history of the child supplied by the mother, and a review of medical records for confirmation of illnesses. We made up a standard physical, with some special attention to liver and spleen size and rashes. Besides a regular medical history, we were interested in breast-feeding success and duration. In order to reduce the biases in comparisons between breast-fed and bottle-fed groups, we wanted to be able to separate out children who had switched to the bottle because they had not been doing well at the breast. Thus we had several questions on when weaning had begun and ended, and why. In addition to our own history, we also made up a standard form for review of the child's medical record.

Measurement of effects on the central nervous system is difficult, however. For use in newborns, there were two reasonably standardized scales: the Prechtl neurological exam (*40*) and the Brazelton Neonatal Behavioral Assessment Scale (*41*). The Prechtl exam, although extremely detailed and rigorous, required a physician, preferably a pediatrician, and preferably one who had trained with Prechtl in its use. The Brazelton was in use by nurses and physical therapists, had been used under a variety of conditions for research, and had good reliability. It was sensitive to prematurity, to drugs like anesthetics given intrapartum, and to the withdrawal state in children of mothers addicted to narcotics. There was, however, not sufficient experience with it to be confident about its ability to predict later dysfunction, except perhaps at extremes. It was time-consuming to administer and did not produce a single number, but rather scores on a series of scales. We chose to use the Brazelton. For children from 6 months to 2 years, the only serious candidate instrument was the Bayley Scales of Infant Development (*42*), which has wide acceptance as a research tool and with which there is experience and familiarity. It generates two numbers, a motor and a mental developmental index. Children graduate from the Bayley at age three; one can then use one of several standard IQ tests. However, experience had begun to accrue with the McCarthy Scales of Children's Abilities (*43*), a school readiness test with six scales relating to both mental and motor abilities, which seemed to be relatively free of strong cultural influence. These scales did not have the standardization data available that the IQ tests had, but we were persuaded by their other features to use them.

Initially, we set our period of follow-up as 6 months, because it was our belief that almost all breast-feeding would be during that time, and because we were originally only concerned about short-term effects. As it turned out, among the women whom we followed, breast-feeding often extended well beyond 6 months, at least to the extent of a nursing morning and night. We eventually decided to extend the study to 5 years. Another necessary decision was sample size. We were interested in multiple outcomes and had a group whose exposures were changing over time, so we could not calculate a single number that would give us a specified power to detect important associations and declare them statistically significant. We tried to decide what comparisons would be the most difficult to make and to ensure that we would have enough children available for

them, although it turned out later that our guesses about the breast-feeding practices and contaminant levels of these women were not very good. The sample sizes we got from this exercise were then decreased rather substantially to accord with the practical constraints of the number of births available in the area and the percentage of women who could be induced to volunteer for this rather time-consuming study. We finally decided that about 300 women each from three centers would be a reasonable goal.

The first baby enrolled in the study was born in April 1978, and the 856th and final one in October 1982. We recruited volunteers from three sources in North Carolina: The Durham Women's Clinic, a large suburban group practice, the Wake County Area Health Education Center, a university-affiliated group providing medical faculty and other services to the Wake County Hospital in Raleigh, and the Department of Pediatrics of the East Carolina University School of Medicine in Greenville. Families were found through hospital tour presentations, through Lamaze and prepared childbirth classes, and to some extent by word of mouth. At or near term, mothers gave written consent and were given a questionnaire. During the admission for labor and delivery, we collected maternal blood, cord blood, placenta, and a sample of whatever the child was eating (colostrum/early milk or formula). We examined the child, performed the Brazelton, and reviewed the obstetric and nursery record. We saw the child again at 6 weeks, did a physical, obtained the child's medical history, and collected blood and breast milk or formula. There was a similar visit at 3 months, except that we no longer collected maternal blood. At 6 months, the Bayley scales were done, and a new consent for further follow-up was signed. There are visits at 1 year, 18 months, 2 years, and then yearly; they consist of a history and physical, medical and hospital record review, and Bayley or McCarthy scales. Breast milk is collected as long as the mother is lactating. The final visit is at 5 years of age. We are now converting to a registry for follow-up, and will keep a current file of names and addresses through a yearly mail or phone contact.

The North Carolina Project: Preliminary Findings

We have extended or confirmed a variety of findings from these data, as well as making some new observations. The expected, almost universal, contamination of milk by PCBs and DDE was confirmed. Our numbers in North Carolina appear to be somewhat higher than national (*2*) or Michigan (*44*) numbers for PCBs. We find no relationship between age, race, reported occupation, or cigarette smoking and PCBs; regular alcohol use is associated with somewhat higher levels. DDE goes up with age and is higher in blacks and smokers. Values for both chemicals decline over the course of lactation; on the average, values at 6 months are about 20% lower than in the beginning of lactation. Both chemicals are about 3-fold higher in maternal term blood than in cord blood. We were unable to confirm an association between these chemicals and prematurity (*45,46*); for both chemicals, the correlation with birth weight is essentially zero. This is not because our study is too small; we were able to show readily the familiar 200-g decrement in birth weight associated with smoking. Mothers whose children are jaundiced or who are treated for jaundice do not have higher levels, and overall stay in the hospital is the same across all levels.

Women with higher levels of DDE tend not to breast-feed as long; those in the top 5% for DDE have a median duration of breast-feeding of 9 weeks, while those in the bottom 6% breast-feed 35 weeks. This relationship is not an artifact of age, since older women tend to breast-feed longer in spite of their higher DDE levels. Neither is it due to parity or race; we restricted the analysis to whites, and the same result holds for first-borns only. Socioeconomic status is difficult to measure in this group of families, but we appear to have little variability. Women with higher levels report more often an early weaning for reasons like "not enough milk" or "difficulty feeding"; thus it does not appear that the relationship is an artifact due to women who must leave the home having higher levels. The concentration of PCBs does not appear to be related to duration of breast-feeding.

Reduction in the length of time spent breast-feeding is consistent either with an effect on the child or on the mother. If milk with higher levels of contaminants fails to provide a full measure of immunologic protection or basic nutrition, the children would tend not do as well and thus be supplemented or weaned earlier. Basically this is the mechanism we proposed might operate when we designed the study, and we are now looking at illnesses, weight gain, and development. However, in the children exposed to the higher levels of contamination, lactation time tends to be short, so it is not clear that we will be able to see such an effect even if it is present.

A maternal effect is an alternative explanation. One possibility is that it is mediated through an estrogenic effect. Certain PCB congeners are estrogenic, as is *o,p*-DDE. Although they are very weak on a mole-to-mole basis compared with estradiol or DES, they are persistent (*47*) and thus might interact with estrogen receptors over a long period of time and lead to the expression of an effect at low doses. There are no directly applicable laboratory data on this question. However, kepone, a compound that shares some structure with PCBs and DDE, can be shown to be an active estrogen in a mouse system at very low doses if the duration of exposure is long and the chemical is allowed to accumulate (*48*). In addition, the administration of certain PCB mixtures in rats induces altered liver metabolism of estrogens and can result in a uterine weight response that is different from controls. We are currently discussing the feasibility of an animal model

in which duration of lactation as measured endocrinologically and histopathologically is used as an endpoint. There are no studies in which this phenomenon has been examined in detail in common laboratory species, such as the mouse or the rat, as a toxicological endpoint. The substantial literature on lactation in dairy animals is related mostly to endocrine responses.

Other Ideas

Various conditions of unknown etiology which might be related to these chemicals have been described in children. While none of them are totally plausible as the assured outcome of contaminated milk, the measurement of contaminants might be done in the context of another etiologic study. One such condition is late-occurring breast-milk jaundice. Although incidence figures are hard to get, the condition is too rare for a study like ours to have many cases. As mentioned above, the physiologic mechanism of unconjugated hyperbilirubinemia at 3 to 12 weeks is thought to be the presence of a pregnanediol that inhibits glucuronyltransferase. However, only about 70% of the children with this condition have appreciable amounts of hormone in their milk, and thus a reasonable study might involve either looking at the milks of those who did not have the hormone or looking at all cases for an interaction with the hormone.

Several skin diseases might represent cases of chemical toxicity. The pigmented spots noted by Harlap (*49*) or neonatal pustular melanosis (*50*) might be a mild form of the neonatal chloracne seen in Yusho. In neither of these conditions is the frequency of breast-feeding noted in the reports describing the cases, and thus a necessary first step would be the establishment of that relationship. Eczema, on the other hand, has now been reported in several different studies to be more frequent among breast-fed children (*22*), and the suggestion has been made that this may represent the effect of contaminant chemicals. Eczema has not been shown to be associated with these chemicals in outbreaks of illness, but it would be easy to study and has some plausibility.

Finally among these sorts of studies, the issue of failure to thrive at the breast might be studied in case-control fashion, to see whether women who report this condition are at an extreme. Based on animal studies, this is quite a plausible outcome of several of the chemicals in question, most notably PCBs.

Given that one has access to a large number of children on whom milk analyses have been done, a variety of studies are possible in which one can compare those with the highest and lowest exposures. At the moment, the most sensitive of the feasible studies based on laboratory work is the caffeine breath test (*51,52*). Caffeine-*o*-demethylase is a P-448 enzyme that is readily induced by environmentally occurring polycyclic hydrocarbons; it is most strongly induced by methylcholanthrene, but it is also induced by PCBs. The test measures the metabolism of caffeine by counting radiolabeled CO_2 in expired air. The amount of radiation exposure is small, the test is reproducible, and it has been shown to be sensitive to cigarette smoking. Antipyrine clearance has been shown to be altered in adults who work around PCBs (*53*), but antipyrine clearance studies require serial blood measurements and are really best done on an inpatient basis. The breath test should be suitable for use in outpatient children.

Discussion

We think that lactation offers a variety of opportunities to investigate either exposure to environmental chemicals or their toxicity in a group that might be among the most susceptible of humans because of their rapid growth, immaturity of metabolism, and limited diets. There are few groups now working in the area because the studies are difficult. Participation is time-consuming and tedious for the mother, and the chemical analytic procedures are expensive, cumbersome and subject to contamination. However, as more focused ideas are studied and as laboratory measures improve, perhaps by the field applicability of a radioimmunoassay for PCB, the sparse literature should grow and the nonspecific anxieties generated by reports of pollutants in milk should be replaced by realistic consideration of plausible toxicity based on good data.

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